UDC 54.057+547.853+547.677

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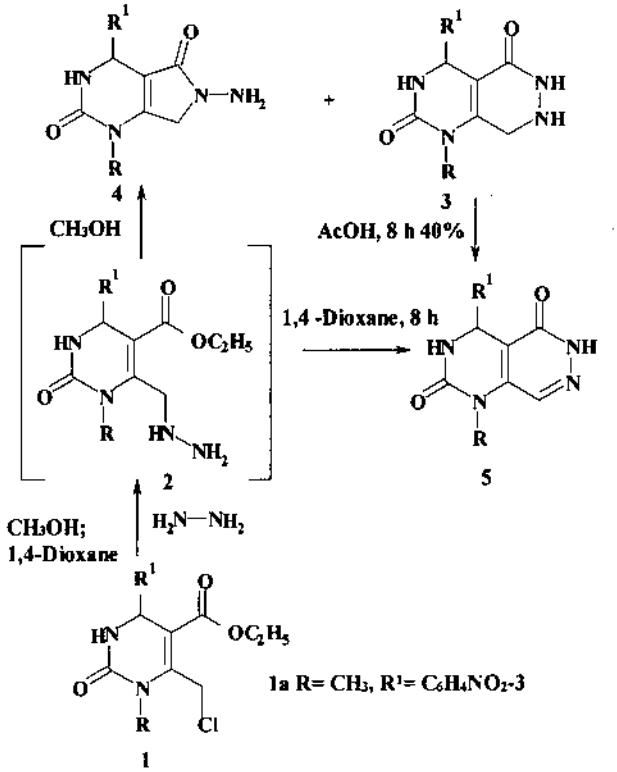
INTERACTION OF 4-SUBSTITUTED 5-CARBETHOXY-6-CHLOROMETHYLPYRIMIDIN-2-ONES WITH HYDRAZINES AND HYDRAZIDE DERIVATIVES: SYNTHESIS AND STRUCTURE *

Reaction of 5-carbethoxy-6-chloromethyl-3,4-dihydropyrimidin-2(1*H*)-ones with N,N'-binucleophiles has been studied on hydrazine hydrate, monosubstituted hydrazines and carboxylic acid hydrazides. It has been determined that the reaction takes place as nucleophilic substitution of halogen on N,N'-binucleophile followed by the primary pyrimidine heterocyclisation into the pyrrolo[4,3-*d*]pyrimidine and pyridazino[4,5-*d*]pyrimidine derivatives.

INTRODUCTION. 3,4-Dihydropyrimidin-2(1*H*)-ones (DHPMs) obtained *via* Biginelli reaction are thoroughly studied these days due to the wide spectrum of their biological activity. In particular, DHPMs possess high efficiency against cardiovascular disorders [1], cancer affected cells [2]. Biginelli compounds belong to the azaanalogs of the Hantzsch 1,4-dihydropyridine calcium channel modulators of Nifedipine, Nacardipine, Amlodipine type [3]. The strategy of Biginelli reaction is applied to obtain synthetic analogs of Batzelladines A-D — potent HIV inhibitors [4]. However, being also of a practical interest, ring-condensed DHPM derivatives have been much less studied which explains with only a few works devoted to this subject [5, 6].

The most convenient synthetic approach towards condensed DHPMs is a cyclocondensation of 5-alkoxycarbonyl-6-halomethyl DHPMs with the variety of N-, O- , S-nucleophilic reagents which allows forming partially hydrogenated condensed azolopyrimidine systems. Thus, the library of substituted tetrahydropyrrolo[4,3-*d*]pyrimidine-2,5-diones has been synthesized in such a way. The study of their biological activity has shown that such compounds are the perspective objects of pharmaceutical and agricultural screening [7]. In this paper the research has been extended employing such N,N'-binucleophilic reagents as hydrazine, hydrazide and their monoalkyl (aryl, acyl) substituted analogs employed in the heterocyclization process of initial DHPMs.

The first question on the heterocyclisation considered at this work concerns its regioselectivity. Previous data [5, 6] revealed that on the first stage of the heterocyclization process, nucleophilic attack on the halomethyl moiety takes place leading to the formation of corresponding 6-aminomethyl DHPMs (compound 2, scheme 1):



Scheme 1.

Such heterylamines bearing alkoxycarbonyl group at *ortho*-position are rather unstable, thus, they easily undergo the second stage of heterocyclization forming a new annelated azine ring (compound 3, scheme 1).

* This work was supported by Fundamental Researchers State Fund (F25.3/023).

It should be noted that the regioselectivity of condensed bicyclic five-membered DHPMs' formation is well-defined for the systems where the new heterocycle obtaining employs mononucleophilic reagents [5—7]. As nucleophilic compounds with a few reactive centers are employed in the reaction it is rather complicated to envisage the regioselectivity of the process, thus additional research on the structure of the final compounds is required. Previous data [5, 6] report on highly regioselective heterocyclization of 6-halomethyl 5-carbethoxyDHPMs into 4,6,7,8-tetrahydropyrimido[4,5-*d*]pyridazine-2,5(1H,3*H*)-diones (compound 3, scheme 1) upon their treatment with hydrazine and its monosubstituted analogs. At this work the reaction mixtures under different reaction conditions were studied to follow the final products' formation. LC/MS data for the condensation of compound 1a with an excess of hydrazine hydrate has revealed the formation of all three products (compounds 3a, 4a, 5, scheme 1) at different amount depending on the reaction conditions. Condensation of compound 1a with hydrazine hydrate at MeOH for 8 h revealed 70 % of mixture compounds 3a and 4a. The analogous condensation in 1,4-dioxane revealed 15 % of compounds 3a, 4a isomers' mixture and 43 % of compound 5. Dihydropyrimido[4,5-*d*]pyridazine-2,5(1*H*,3*H*)-dione (5) was also formed at the amount of 40 % as compound 3a was refluxed in acetic acid for 8 h. The structure of molecule 5 (fig. 1) was determined with X-ray diffraction experiments, ^{1}H NMR, IR, elemental analysis data (see experimental part for details). We suggest that the formation of HC=N bond is explained by the mobility of the 6-C methylene group protons which has been previously studied [8].

The heterocyclization process of compounds 1a–d with hydrazines or carboxylic acid hydrazides (EtOH or 2-PrOH, reflux, 6–8 h) using TEA (triethylamine) as catalyst leads to the formation of the mixture of pyrimido[4,5-*d*]pyridazine-2,5-diones (3) (scheme 2) and products of monosubstitution — 6-aminoalkyl DHPMs (7) (scheme 2) (up to 50 %). It should be noted that multiple tries to put the compound 7 into the further heterocyclization to obtain bicyclic DHPMs of 4 or 8 type (scheme 2) failed. Moreover, the attempts aimed at the cyclisation of symmetrically substituted hydrazides and hydrazines with DHPMs were not successful either. The reaction did not take place even under harsh conditions (DMF, reflux, 8 h, or sealed tube, 100—120 °C).

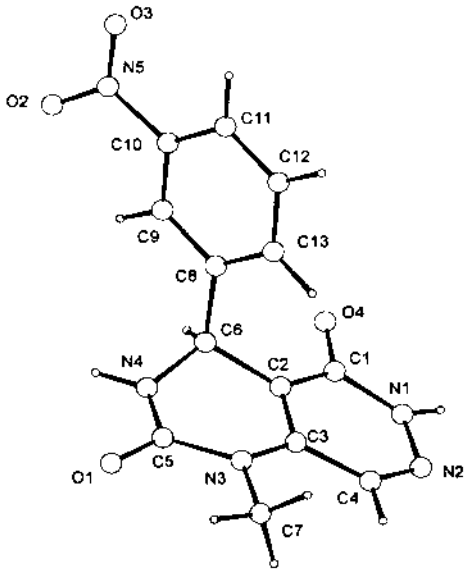
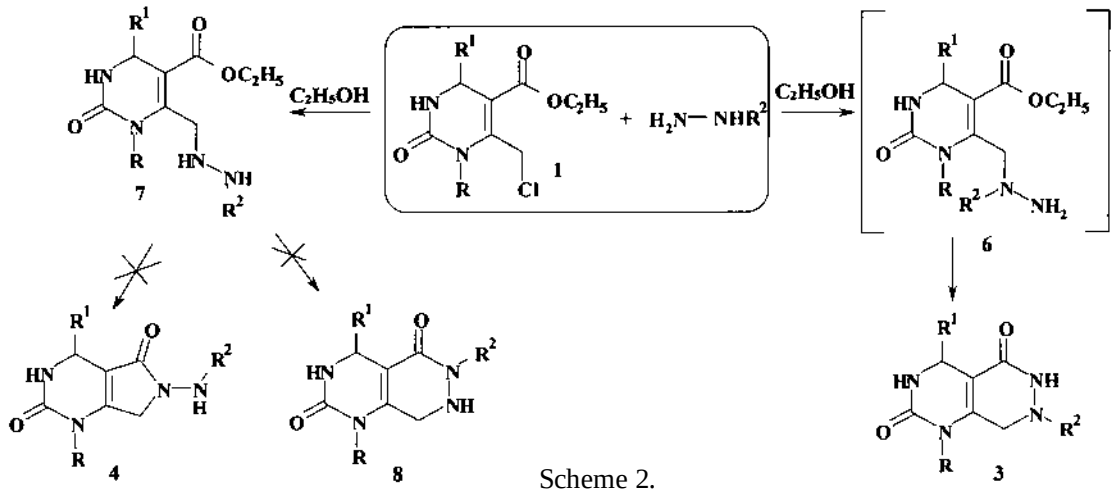


Fig. 1. Perspective view and labeling scheme for the molecule 5.



Scheme 2.

The structure of compound 3h was confirmed with ^{1}H NMR, ^{13}C NMR, COSY, NOESY and HETCOR data. Having used these methods we fully correlated chemical shifts of ^{1}H NMR and ^{13}C NMR spectra. Hence, in ^{1}H NMR spectrum the chemical shift of CONH group proton is δ 10.01 ppm. It is

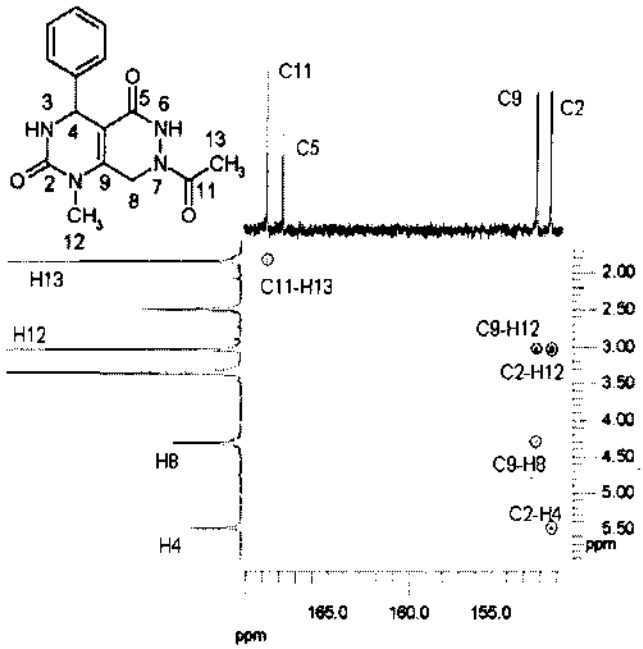


Fig. 2. Fragment of compound 3h 2D long-range HETCOR experiment.

possible only when the compound has the structure type of compound 3. In other cases (compounds 4, 8) the signal of NH protons should be expected in a stronger field. Analogous shift of CONH group proton was determined in all compounds 3 of the presented library. Additionally, 2D long-range HETCOR experiment (fig. 2) did not reveal spin-spin interaction of carbon C5 with protons H8 which may take place in case of the six-membered pyridazine ring (3) rather than the five-membered one (4). The carbon spectrum was taken with the interrupted-proton decoupling (splitted spectrum from NOE) together with carbon spectra with selective decoupling of H8 protons to determine distant heteronuclear proton-carbon coupling constants. The absence of carbonyl C5 decoupling on the protons of methylene group H8 was determined.

It should be mentioned that in some cases the signal of chiral 4-CH of DHPMs (1a–d) and their derivatives 3, 7 is presented with a broadened pseudo-singlet whereas splitted on 3-NH doublet is expected to take place (tabl. 1–3). The signals of IR spectra for C=O, and N–H groups of compounds 1a–d and 3, 5, 7 are broadened in most cases due to the intramolecular bonds of C=OEN–H (tabl. 1–3).

A library of 7-substituted tetrahydropyrimido[4,5-*d*]pyridazine-2,5-diones (3b–s) was synthesized by interaction of halomethyl DHPMs (1a–d) with a series of N,N'-nucleophiles. It was revealed that with the change of reaction conditions (e.g. solvent system, reaction time) the *ratio* of the final products changes dramatically. Thus, as nucleophiles with a few reaction centres employed in the reaction process it is suggested to study the reaction conditions as well as reaction mixtures in more detail. The structure of the obtained compounds has been unambiguously determined with the single crystal X-ray diffraction analysis, NMR (^{1}H, ^{13}C, COSY, NOESY, HETCOR), LC/MS, elemental analysis and IR spectroscopy.

EXPERIMENTAL PART. All chemicals were obtained from commercial sources and used without further purification. Melting points (mp) were measured on an electrothermal capillary melting point apparatus and are uncorrected. IR spectra were recorded with a UR-20 spectrophotometer (KBr platelets). ^{1}H NMR spectra (400 MHz) were recordered on a Varian GEMINI 2000 spectrometer using DMSO-d_6 as solvent and TMS as internal standard. ^{1}H–^{1}H COSY spectra were acquired into 2048 (F2) and 512 (F1) time-domain data matrix and 2048 (F2)x2048 (F1) frequency-domain matrix after zero-filling. NOESY spectra were acquired with parameters similar to COSY spectra. Mixing times were determined preliminary from T_1-measurement experiment for each sample by conventional inversion-recovery method. Heteronuclear chemical shift correlation (HETCOR) was used for determine ^{1}H–^{13}C attachment with the 2048 (F2)x256 (F1) time-domain matrix and 2048 (F2)x1024 (F1) frequency-domain matrix after zero-filling. The average value of one bond constant J_{CH} was set to 140 Hz. HETCOR for determination long range correlation had very similar parameters and average value of mulitibond C–H coupling constant was set to 8 Hz. HPLC-MS was carried out on a system consisting of an Agilent 1100 Series high-pressure liquid chromatograph equipped with a diode matrix and Agilent LC/MSD SL mass-selective detector. HPLC-MS parameters: column: Zorbax SB-C18, 1.8 μm, 4.6x30 mm; solvents: MeCN–H_2O (95:5), 0.1 % TFA; eluent flow: 3 mL·s^{-1}; injected sample volume: 1 μL; UV detector: λ = 215, 254, 265 nm; ionization method: chemical ionization under atmospheric pres-

Table 1

6-Chloromethyl-2-oxo-4-aryl-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl esters 1a–d

Compound	R	R^1	mp, °C	Yield, %	NMR ^1H (400 MHz, DMSO-d_6), ppm	IR (KBr platelets), cm^{-1}	Elemental analyses data, %	
							Calculated	Found
1a	CH_3	$C_6H_4NO_2$-3	153–154	89	δ = 8.33 [*d*, ^3J(H,H)=2.8 Hz, 1 H, NH], 8.14 [*m*, 2 H, Ar], 7.67 [*m*, 2 H Ar], 5.36 [*d*, ^3J(H,H)=3.2 Hz, 1 H, *CH*NH], 5.19 [*d*, ^3J(H,H)=11.6 Hz, 1 H, CH_2Cl], 5.01 [*d*, ^3J(H,H)=11.6 Hz, 1 H, CH_2Cl], 4.10 [*q*, ^3J(H,H)=6.4 Hz, 2 H, CH_2CH_3], 3.23 [*s*, 3 H, NCH_3], 1.13 [*t*, ^3J(H,H)=6.8 Hz, 3 H, CH_2CH_3]	1350, 1540 (NO_2); 1605 (C=C); 1670, 1740 (C=O); 3280 (NH)	C 50.93; N 11.88	C 50.92; N 11.90
1b	H	Ph	152–153	76	δ = 9.50 [*s*, 1 H, NH], 7.85 [*br.s*, 1 H, NH], 7.30 [*m*, 5 H, C_6H_5], 5.19 [*d*, ^3J(H,H)=8.0 Hz, 1 H, *CH*NH], 4.78 [*d*, ^2J(H,H)= =10.8 Hz, 1 H, CH_2Cl], 4.58 [*d*, ^2J(H,H)=10.8 Hz, 1 H, CH_2Cl], 4.03 [*q*, ^3J(H,H)=6.8 Hz, 2 H, CH_2CH_3], 1.11 [*t*, ^3J(H,H)= =6.8 Hz, 3 H, CH_2CH_3]	1630 (C=C); 1680 (C=O); 3340 (NH)	C 57.05; N 9.50	C 57.03; N 9.52
1c	CH_3	Ph	144–145	81	δ = 8.14 [*d*, ^3J(H,H)=3.2 Hz, 1 H, NH], 7.34 [*t*, ^3J(H,H)= =7.2 Hz, 2 H, 3-, 5-H Ph], 7.26 [*t*, ^3J(H,H)=7.2 Hz, 2 H, 4-, 2-H Ph], 7.23 [*d*, ^3J(H,H)=7.6 Hz, 1 H, 6-H Ph], 5.19 [*m*, 2H, NH*CHC* H_2Cl overlapped], 5.00 [*d*, ^3J(H,H)=12 Hz, 1 H, NH*CH*], 4.10 [*q*, ^3J(H,H)=6.8 Hz, 2 H, CH_2CH_3], 3.22 [*s*, 3 H, NCH_3], 1.12 [*t*, ^3J(H,H)=7.2 Hz, 3 H, CH_2CH_3]	1610 (C=C); 1670 (C=O); 3230 (NH)	C 58.35; N 9.07	C 58.31; N 9.09
1d	CH_3	$C_6H_4OCH_3$-4	110–111	80	δ = 8.06 [*d*, ^3J(H,H)=3.2 Hz, 1 H, NH], 7.14 [*d*, ^3J(H,H)= =8.4 Hz, 2 H, Ar], 6.89 [*d*, ^3J(H,H)=8.4 Hz, 2 H, Ar], 5.08 [*m*, 3 H, NH*CH* CH_2Cl overlapped], 4.09 [*m*, 2 H, CH_2CH_3], 3.72 [s, 3 H, OCH_3], 3.21 [s, 3 H, NCH_3], 1.15 [*t*, ^3J(H,H)= =6.8 Hz, 3 H, CH_2CH_3]	1610 (C=C); 1670 (C=O); 3290 (NH)	C 56.72; N 8.27	C 56.72; N 8.26

Table 2

7-Substituted-4-aryl-4,6,7,8-tetrahydro-1*H*,3*H*-pyrimido[4,5-*d*]pyridazine-2,5-diones 3b–s

Compound	R	R^1	R2	mp, °C	Yield, %	NMR ^1H (400 MHz, DMSO-d_6), ppm	IR (KBr platelets), cm^{-1}	Elemental analyses data, %	
								Calculated	Found
3b	CH_3	$C_6H_4NO_2$-3	CH_2CH_2OH	208–209	44	δ = 8.72 [*s*, 1 H, NNH], 8.13 [*s*, 1 H, NH], 8.09 [*d*, ^3J(H,H)=8.0 Hz, 1 H, H6 Ar], 7.97 [*d*, ^4J(H,H)=2.8 Hz, 1 H, H2 Ar], 7.75 [*d*, ^3J(H,H)= =7.6 Hz, 1 H, H4, Ar], 7.61 [*m*, 1 H, H5 Ar], 5.37 [*d*, ^3J(H,H)=3.6 Hz, 1 H, *CH*NH], 4.44 [*t*, ^3J(H,H)=5.2 Hz, 1 H, OH], 4.07 [*m*, 2 H,	1350, 1530 (NO_2); 1630 C=C; 1650, 1690 (CO); 3290 (NH); 3455 (OH)	C 51.87; N 20.16	C 51.85; N 20.14

Continuation table 2

Compound	R	R^1	R2	mp, °C	Yield, %	NMR ^{1}H (400 MHz, DMSO-d_6), ppm	IR (KBr platelets), cm^{-1}	Elemental analyses data, %	
								Calculated	Found
						CH_2], 3.46 [*m*, 2 H, CH_2OH], 3.08 [*s*, 3 H, CH_3], 2.79 [*m*, 2 H, $NHCH_2$]			
3c	H	Ph	$C_6H_4CH_3$-4	225	87	δ = 9.48 [*s*, 1 H, NH], 9.22 [s, 1 H, NH], 7.62 [*br.s*, 1 H, NNH], 7.13 [*m*, 3 H, Ar], 7.03 [*d*, ^3J(H,H)=8.4 Hz, 2 H, Ar], 6.90 [*d*, ^3J(H,H)=7.2 Hz, 2 H, Ar], 6.79 [*d*, ^3J(H,H)= =8.4 Hz, 2 H, Ar], 5.15 [*br. pseudo-s*, 1 H, *CH*NH], 4.35 [*s*, 2 H, CH_2], 2.24 [*s*, 3 H, CH_3]	C=C 1620; C=O 1650; NH 3360	C 68.25; N 16.76	C 68.24; N 16.68
3d	H	Ph	$C_6H_4OCH_3$-4	134–135	79	δ = 9.99 [*s*, 1 H, NH], 7.82 [*br.s*, 1 H, NH], 7.75 [*d*, ^3J(H,H)=8.0 Hz, 1 H, Ar], 7.53 [*m*, 1 H, Ar], 7.32 [*m*, 5 H, C_6H_5], 7.16 [*d*, ^3J(H,H)=8.0 Hz, 1 H, Ar], 7.06 [*m*, 1 H, Ar], 5.25 [*br. pseudo-s*, 1 H, *CH*NH], 4.38 [*m*, 2 H, CH_2], 3.89 [*s*, 3 H, OCH_3], 3.07 [*s*, 3 H, NCH_3]	1605 (C=C); 1650 (C=O); 3310 (NH)	C 65.13; N 15.99	C 65.11; N 15.97
3e	CH_3	Ph	C_6H_4COOH-4	132–135	8	δ = 10.67 [*s*, 1 H, COOH], 7.85 [*m*, 3 H, Ar, NH], 7.6 [*m*, 1 H, Ar], 7.51 [*m*, 2 H, Ar], 7.25 [*d*, ^3J(H,H)=8.8 Hz, 2 H, Ar], 6.91 [*d*, ^3J(H,H) =8.8 Hz, 2 H, Ar], 5.20 [*r pseudo-s*, 1 H, *CH*NH], 4.41 [*m*, 2 H, CH_2], 3.74 [*s*, 3 H, NCH_3], 3.06 [*s*, 3 H, CH_3]	1605 (C=C); 1670 (C=O); 3360 (NH), 3430 (COOH)	C 63.49; N 14.81	C 63.49; N 14.82
3f	CH_3	$C_6H_4NO_2$-3	C_6H_4COOH-2	289–290	84	δ = 13.2 [*br.s*, 1 H, COOH], 9.12 [*s*, 1 H, NNH], 8.21 [*s*, 1 H, NH], 8.17 [*d*, ^3J(H,H)= =8.0 Hz, 1 H, Ar], 8.03 [*s*, 1 H, Ar], 7.87 [*d*, ^3J(H,H)=8.1 Hz, 1 H, Ar], 7.81 [*d*, ^3J(H,H)= =8.0 Hz, 1 H, Ar], 7.69 [*m*, 1 H, Ar], 7.38 [*m*, 1 H, Ar], 6.77 [*m*, 1 H, Ar], 6.72 [*d*, ^3J(H,H)= =8.0 Hz, 1 H, Ar], 5.51 [*br. pseudo-s*, 1 H, *CH*NH], 4.46 [*s*, 2 H, CH_2], 3.06 [*s*, 3 H, CH_3]	1320, 1540 (NO_2); 1605 (C=C); 1670 (C=O); 3200 (NH); 3310–3320 (COOH)	C 56.74; N 16.54	C 56.72; N 16.55
3g	CH_3	$C_6H_4NO_2$-3	$C_6H_3NO_2$-2,4	210–212	56	δ = 10.21 [*s*, 1 H, CH_2NH], 8.24 [*m*, 5 H, Ar], 7.88 [*m*, 1 H, Ar], 7.70 [*m*, 1 H, Ar], 7.31 [*d*, ^3J(H,H)=8.0 Hz, 1 H, Ar], 5.56 [*br. pseudo-s*, 1 H, *CH*NH], 4.47 [*m*, 2 H, CH_2], 3.09 [*s*, 3 H, NCH_3]	1310, 1345 (NO_2), 1590; 1605 (C=C); 1660, 1710 (C=O); 3320 (NH)	C 48.62; N 20.89	C 48.61; N 20.87
3h	CH_3	Ph	CO-CH_3	208–209	80	δ = 9.92 [*s*, 1 H, NNH], 7.80 [*s*, 1 H, NH], 7.30 [*m*, 5 H, C_6H_5], 5.21 [*br. pseudo-s*, 1 H, *CH*NH], 4.25 [*m*, 2 H, CH_2], 3.03 [*s*, 3 H, NCH_3], 1.86 [*s*, 3 H, $COCH_3$]	1595 (C=C); 1650, 1705 (C=O); 3230 (NH)	C 59.99; N 18.66	C 55.96; N 18.65

Continuation table 2

Compound	R	R^1	R2	mp, °C	Yield, %	NMR ^1H (400 MHz, DMSO-d_6), ppm	IR (KBr platelets), cm^{-1}	Elemental analyses data, %	
								Calculated	Found
3i	CH_3	$C_6H_4OCH_3$-4	CO-C_6H_5	210–211	81	10.63 [*s*, 1 H, NNH], 7.88 [*d*, ^3J(H,H)=7.6 Hz, 2 H, Ar], 7.80 [*br.s*, 1 H, CH*NH*], 7.60 [*m*, 1 H, Ar], 7.51 [*m*, 2 H, Ar], 7.26 [*d*, ^3J(H,H)=8.0 Hz, 2 H, $C_6H_4OCH_3$], 6.91 [*d*, ^3J(H,H)=8.0 Hz, 2 H, $C_6H_4OCH_3$], 5.22 [*br. pseudo-s*, 1 H, *CH*NH], 4.41 [*m*, 2 H, CH_2], 3.71 [*s*, 3 H, OCH_3], 3.07 [*s*, 3 H, NCH_3]	1620 (C=C); 1670, 1710 (C=O); 3270 (NH)	C 64.28; N 14.28	C 64.26; N 14.28
3j	H	Ph	CO-$C_6H_4CH_3$-4	123–125	84	δ = 9.45 [*s*, 1 H, NH], 9.20 [*s*, 1 H, NH], 7.59 [*br.s*, 1 H, NH], 7.13 [*m*, 3 H, Ar], 7.03 [*d*, ^3J(H,H)=8.0 Hz, 2 H, Ar], 6.91 [*d*, ^3J(H,H)=8.0 Hz, 2 H, Ar], 6.80 [*d*, ^3J(H,H)=8.0 Hz, 2 H, Ar], 5.16 [*br. pseudo-s*, 1 H, *CH*NH], 4.35 [*m*, 2 H, CH_2], 2.24 [*s*, 3 H, CH_3]	1600 (C=C); 1640, 1690 (C=O); 3440 (NH)	C 66.29; N 15.46	C 66.26; N 15.45
3k	CH_3	$C_6H_4OCH_3$-4	CO-$C_6H_4OCH_3$-3	148	88	δ = 10.63 [*s*, 1 H, NNH], 7.84 [*br.s*, 1 H, NH], 7.40 [*m*, 3 H, C_6H_4-OCH_3-*m*], 7.14 [*d*, 2 H, H2 H6 C_6H_4-OCH_3-*p*], 7.15 [*m*, 1 H, CH C_6H_4-OCH_3-*m*], 6.91 [*d*, 2 H, H3 H5 C_6H_4-OCH_3-*p*], 5.20 [*br. pseudo-s*, 1 H, *CH*NH], 4.41 [*m*, 2 H, CH_2], 3.79, 3.72 [*ss*, 3 H, 3 H, OCH_3], 3.36 [*s*, 3 H, NCH_3]	1590 (C=C); 1690 (C=O); 3410 (NH)	C 62.55; N 13.26	C 62.52; N 13.27
3l	CH_3	$C_6H_4NO_2$-3	CO-$C_6H_4OCH_3$-2	209	82	δ = 10.03 [*s*, 1 H, NNH], 8.23 [*s*, 1 H, NH], 8.17 [*d*, ^3J(H,H)=8.0 Hz, 1 H, Ar], 8.01 [*br.s*, 1 H, Ar], 7.87 [*d*, ^3J(H,H)=8.0 Hz, 1 H, Ar], 7.74 [*d*, ^3J(H,H)=8.0 Hz, 1 H, Ar], 7.69 [*m*, 1 H, Ar], 7.52 [*d*, ^3J(H,H)=8.0 Hz, 1 H, Ar], 7.16 [*d*, ^3J(H,H=8.0 Hz, 1 H, Ar], 7.06 [*m*, 1 H, Ar], 5.53 [*pseudo-s*, 1 H, *CH*NH], 4.41 [*m*, 2 H, CH_2], 3.88 [*s*, 3 H, OCH_3], 3.09 [*s*, 3 H, NCH_3]	1360, 1530 (NO_2); 1600 (C=C); 1650, 1690 (C=O); 3350 (NH)	C 57.66; N 16.01	C 57.65; N 16.00
3m	CH_3	$C_6H_4NO_2$-3	CO-C_6H_4 OH-3	268	78	δ = 10.50 [*s*, 1 H, OH], 9.59 [*s*, 1 H, NNH], 8.23 [*s*, 1 H, NH], 8.14 [*d*, ^3J(H,H)=8.0 Hz, 1 H, Ar], 8.02 [*br.s*, 1 H, Ar], 7.86 [*d*, ^3J(H,H)=7.6 Hz, 1 H, Ar], 7.66 [*m*, 1 H, Ar], 7.23 [*m*, 3 H, Ar], 6.92 [*d*, ^3J(H,H)=7.6 Hz 1 H, Ar], 5.50 [*br. pseudo-s*, 1 H, *CH*NH], 4.39 [*m*, 2 H, CH_2], 3.08 [*s*, 3 H, CH_3]	1320, 1520 (NO_2); 1610 (C=C); 1650, 1690 (C=O); 3280 (NH)	C 56.74; N 16.54	C 56.72; N 16.55
3n	CH_3	$C_6H_4OCH_3$-4	CO-C6H4 OH-2	274	92	δ = 11.65 [*s*, 1 H, OH], 10.60 [*s*, 1 H, NNH], 7.84 [*m*, 2 H, NH, CH Ar], 7.45 [*m*, 1 H, Ar],	1590 (C=C); 1650, 1690	C 61.76, N 13.72	C 61.72, N 13.70

Continuation table 2

Compound	R	R^1	R2	mp, °C	Yield, %	NMR ^1H (400 MHz, DMSO-d_6), ppm	IR (KBr platelets), cm^{-1}	Elemental analyses data, %	
								Calculated	Found
						7.25 [*d*, ^3J(H,H)=8.0 Hz, 2 H, C_6H_4OH], 6.94 [*m*, 4 H, Ar], 5.21 [*br. pseudo-s*, 1 H, *CH*NH], 4.44 [*m*, 2 H, CH_2], 3.74 [*s*, 3 H, OCH_3], 3.06 [*s*, 3 H, NCH_3]	(C=O); 3200 (NH); 3460 (OH)		
3o	CH_3	$C_6H_4NO_2$-3	CO-C_6H_4 OH-2	289–290	79	δ = 11.63 [*br.s*, 1 H, OH], 10.63 [*br.s*, 1 H, NNH], 8.23 [*s*, 1 H, 2 H $C_6H_4NO_2$], 8.17 [*d*, ^3J(H,H)= =8.8 Hz, 1 H, Ar], 8.08 [*br.s*, 1 H, CONH], 7.85 [*m*, 2 H, Ar], 7.69 [*m*, 1 H, Ar], 7.45 [*m*, 1 H, Ar], 6.94 [*m*, 2 H, Ar], 5.55 [*br. pseudo-s*, 1 H, *CH*NH], 4.46 [*m*, 2 H, CH_2], 3.08 [*s*, 3 H, NCH_3]	1355, 1530 (NO_2); 1650, 1710 (C=O); 3280 (NH); 3340 (OH)	C 56.74, N 16.54	C 56.74, N 15.53
3p	CH_3	Ph	CO-$C6H_3$-5-Br-2-OH	261–262	90	δ = 11.75 [*br.s*, 1 H, OH], 10.58 [*br.s*, 1 H, NNH], 7.99 [*d*, ^4J(H,H)=3.4 Hz, 1 H, H6 $C_6H_3Br(OH)$], 7.86 [*br.s*, 1 H, NH], 7.50 [*dd*, ^3J(H,H)=8.8 Hz, ^4J(H,H)=3.4 Hz, 1 H, H4 $C_6H_3Br(OH)$], 7.31 [*m*, 5 H, C_6H_5], 6.90 [*d*, ^3J(H,H)=8.8 Hz, 1 H, H3 $C_6H_3Br(OH)$], 5.26 [*br. pseudo-s*, 1 H, *CH*NH], 4.37 [*m*, 2 H, CH_2], 3.07 [*s*, 3 H, NCH_3]	1590 (C=C); 1640, 1690 (C=O); 3240 (NH); 3325 (OH)	C 52.53, N 12.25	C 52.50, N 12.24
3q	CH_3	$C6H_4NO_2$-3	CO-$C6H_3$-5-Br-2-OH	234	89	δ = 11.65 [*br.s*, 1 H, OH], 10.56 [*s*, 1 H, NNH], 8.22 [*s*, 1 H, NH], 8.17 [*d*, ^3J(H,H)=8.0 Hz, 2 H, Ar], 8.05 [*br.s*, 1 H, Ar], 7.95 [*d*, ^4J(H,H)=2.2 Hz, 1 H, Ar], 7.86 [*d*, ^3J(H,H)=7.5 Hz, 1 H, Ar], 7.69 [*m*, 1 H, Ar], 7.59 [*m*, 1 H, Ar], 6.95 [*d*, ^3J(H,H)=8.1 Hz, 1 H, Ar], 5.54 [*br. pseudo-s*, 1 H, *CH*NH], 4.44 [*m*, 2 H, CH_2], 3.08 [*s*, 3 H, CH_3]	1355, 1530 (NO_2); 1620,1720 (C=O); 3320 (NH); 3350 (OH)	C 47.83, N 13.94	C 47.82, N 13.95
3r	CH_3	Ph	CO-$C6H_4$ NO_2-4	210–211	73	δ = 11.01 [*s*, 1 H, NNH], 8.36 [*d*, ^3J(H,H)=8.8 Hz, 2 H, $C_6H_4NO_2$], 8.23 [*br.s*, 1 H, CH*NH*], 8.17 [*d*, ^3J(H,H)=8.0 Hz, 1 H, Ar], 8.08 [*m*, 3 H, Ar], 7.87 [*d*, ^3J(H,H)=7.6 Hz, 1 H, Ar], 7.69 [*m*, 1 H, Ar], 5.54 [*br. pseudo-s*, 1 H, *CH*NH], 4.47 [*m*, 2 H, CH_2], 3.09 [*s*, 3 H, CH_3]	1330, 1510 (NO_2); 1590 (C=C); 1660 (C=O), 3450 (NH)	C 58.97, N 17.19	C 58.95, N 17.18
3s	CH_3	$C6H_4NO_2$-3	CO-C_6H_4 NO_2-3	128	71	δ = 11.08 [*s*, 1 H, NH], 8.68 [*s*, 1 H, NH], 8.45 [*d*, ^3J(H,H)=7.6 Hz, 1 H, Ar], 8.22 [*m*, 3 H, Ar], 8.08 [*s*, 1 H, NH], 7.86 [*m*, 2 H, Ar], 7.71 [*m*, 1 H, Ar], 5.55 [*br. pseudo-s*, 1 H, NH*CH*], 4.48 [*s*, 2 H, CH_2], 3.09 [*s*, 3 H, CH_3]	1340, 1360 (NO_2), 1520; (C=C) 1610; 1650 , 1690 (C=O); 3250 (NH)	C 53.10, N 18.58	C 53.07, N 18.57

Table 3

Ethyl 2-oxo-4-aryl-6-[(2-arylhydrazino(hydrazido)methyl]-1,2,3,4-tetrahydropyrimidine-5-carboxylates 7a–h

Compound	R	R^1	R^2	mp, °C	Yield, %	NMR ^1H (400 MHz, DMSO-d_6), ppm	IR (KBr platelets), cm^{-1}	Elemental analyses data, %	
								Calculated	Found
7a	H	Ph	CO-C_6H_5	179	81	δ = 8.64 [*s*, 1 H, NH], 8.51 [*s*, 1 H, NH], 7.90 [*s*, 1 H, NH], 7.31 [*m*, 10 H, Ar], 6.85 [*s*, 1 H, NH], 5.27 [*s*, 1 H, NH*CH*], 4.07 [*m*, 2 H, CH_2CH_3], 1.12 [*m*, 3 H, CH_2CH_3]	1600 (C=C); 1690 (C=O); 3290 (NH)	C 63.95; N 14.20	C 63.94; N 14.21
7b	H	Ph	C_6H_4Me-2	214–215	56	δ = 8.64 [*s*, 1 H, NH], 8.51 [*s*, 1 H, NH], 7.90 [*s*, 1 H, NH], 7.31 [*m*, 10 H, Ar], 6.85 [*s*, 1 H, NH], 5.27 [*s*, 1 H, NH*CH*], 4.07 [*m*, 2 H, CH_2CH_3], 1.12 [*m*, 3 H, CH_2CH_3]	1590 (C=C); 1680 (C=O); 3410 (NH)	C 66.30; N 14.73	C 66.28; N 14.73
7c	H	Ph	$C_6H_5CH_2$	95	42	δ = 7.87 [*s*, 1 H, NH], 7.30 [*m*, 13 H, Ar NH], 5.21 [*s*, 1 H, NH*CH*], 4.62 [*m*, 2 H, $NHCH_2$], 3.97 [*m*, 2 H, CH_2CH_3], 1.06 [*t*, ^3J(H,H)=7.2 Hz, CH_2CH_3]	1610 (C=C); 1720 (C=O); 3420 (NH)	C 66.30; N 14.73	C 66.27; N 14.75
7d	H	Ph	C_6H_4OMe-2	104–106	52	10.68 [*s*, 1 H, NH], 8.83 [*s*, 1 H, NH], 8.38 [*s*, 1 H, NH], 7.89 [*s*, 1 H, NH], 7.26 [*m*, 5 H, Ar], 6.88 [*m*, 4 H, Ar], 5.27 [*br.s*, 1 H, NH*CH*], 4.11 [*m*, 2 H, CH_2CH_3], 3.84 [*s*, 3 H, OCH_3], 1.18 [*s*, 3 H, CH_2CH_3]	1590 (C=C); 1710 (C=O); 3330 (NH)	C 63.62; N 14.13	C 63.61; N 14.14
7e	H	Ph	C_6H_4OH-4	171	38	δ = 11.07 [*s*, 1 H, OH], 8.60 [*s*, 1 H, NH], 8.43 [*br.s*, 1 H, NH], 7.89 [*br.s*, 1 H, NH], 7.32 [*m*, 5 H, C_6H_5], 7.16 [*d*, ^3J(H,H)=8.0 Hz, 2 H, C_6H_4OH], 7.06 [*d*, ^3J(H,H)=8.0 Hz, 2 H, C_6H_4OH], 5.56 [*br.s*, 1 H, NH*CH*], 4.07 [*q*, ^3J(H,H)=5.2 Hz, 2 H, CH_2CH_3], 2.23 [*s*, 3 H, NCH_3], 1.16 [*t*, 3 H, CH_2CH_3]	1580 (C=C); 1640, 1660 (C=O); 3350 (NH); 3390 (OH)	C 62.82; N 14.65	C 62.80; N 14.64
7f	CH_3	Ph	C_6H_4OH-2	176–177	44	δ = 10.80 [*br.s*, 1 H, OH], 8.06 [*d*, ^3J(H,H)=2.4 Hz, 1 H, NH*CH*], 7.63 [*d*, ^3J(H,H)=8.0 Hz, 1 H, Ar], 7.51 [*d*, ^3J(H,H)=8.4 Hz, 1 H, Ar], 7.32 [*m*, 6 H, Ar], 7.03 [*m*, 1 H, Ar], 5.95 [*d*, ^3J(H,H)=14.8 Hz, 1 H. CH_2], 5.60 [*d*, ^3J(H,H)=14.8 Hz, 1 H. CH_2], 5.29 [*d*, ^3J(H,H)=3.6 Hz, 1 H, NH*CH*], 4.08 [*m*, 2 H, CH_2CH_3], 2.91 [*s*, 3 H, NCH_3], 1.10 [*t*, ^3J(H,H) = 7.2 Hz, 3 H, CH_2CH_3]	1600 (C=C); 1690 (C=O); 3330 (NH); 3370 (OH)	C 63.62; N 14.13	C 63.61; N 14.15
7g	H	Ph	C_6H_4-COOH-4	141–143	31	δ = 12.4 [*br.s*, 1 H, OH], 11.43 [*s*, 1 H, CONH], 8.72 [*s*, 1 H, NH], 8.62 [*s*, 1 H, NH], 7.83 [*m*, 3 H, NH Ar], 7.30 [*m*, 7 H, Ar], 5.29 [*s*, 1 H, NH*CH*], 4.09 [*q*, ^3J(H,H)=7.2 Hz, 2 H, CH_2CH_3], 1.05 [*t*, ^3J(H,H)=7.2 Hz, 3 H, CH_2CH_3]	1610 (C=C); 1660, 1710 (C=O); 3010 (NH); 3390 (COOH)	C 61.46; N 13.65	C 61.45; N 13.65
7h	H	Ph	CO-C_6H_4 NO_2-4	189–191	51	δ =10.37 [*d*, ^3J(H,H)=5.2 Hz, 1 H, CH*NH*], 9.00 [*s*, 1 H, NH], 8.32 [*d*, ^3J(H,H)=8.8 Hz, 2 H, $C_6H_4NO_2$], 7.99 [*d*, ^3J(H,H)= =8.8 Hz, 2 H, $C_6H_4NO_2$], 7.74 [*br.s*, 1 H, NH], 7.19 [*m*, 5 H, C_6H_5], 5.98 [*d*, ^3J(H,H)=4.8 Hz, 1 H, NH], 5.13 [*br.s*, 1 H, CH*NH*], 4.13 [*m*, 2 H, $NHCH_2$], 3.95 [*q*, ^3J(H,H)= 7.2 Hz, 2 H, CH_2CH_3], 1.06 [*t*, ^3J(H,H)= 7.2 Hz, 3 H, CH_2CH_3]	1340, 1520 (NO_2); 1610 (C=C); 1640, 1660 (C=O); 3350 (NH)	C 57.40; N 15.94	C 57.37; N 15.92

sure (APCI); ionization mode; simultaneous canning of positive and negative ions in *m*/*z* range 100—650. Elemental analysis was performed on Perkin–Elmer C,H,N Analyzer. All crystallographic measurements were performed at room temperature on a Bruker Smart Apex II diffractometer operating in the ω and φ scans mode. Full crystallographic details have been deposited at Cambridge Crystallographic Data Centre (CCDC). Any request to the CCDC for these materials should quote the full literature citation and reference number CCDC757737.

Ethyl 4-aryl-6-(chloromethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates (1a–d) have been synthesized following the described methods [6, 9].

Full physical-chemical data on the compounds 1a–d presented at the tabl. 1.

General procedure for the synthesis of *7-substituted 2-methyl-4-aryl-4,6,7,8-tetrahydropyrimido[4,5-d]pyridazine-2,5(1H,3H)diones (3a–s)* and *ethyl 4-aryl-6-{[2-(substituted) hydrazino(acylhydrazino)]-methyl}-3,4-dihydropyrimidin-2(1H)-one-5-carboxylates (7a–h)*. To suspension of 0.005 mole of 6-chloromethylDHPM (1a–d) in 5—10 mL of EtOH or 2-PrOH, corresponding hydrazine(hydrazide) (0.0075 mole) and TEA (0.5 mL, 0.005 mole) were added and the mixture was refluxed for 8 h. If starting hydrazines or hydrazides were not soluble enough, DMF was added dropwise until the compounds dissolved. The precipitate usually was formed during reflux, in 24 h after cooling the reaction mixture or after the reaction mixture was poured onto crushed ice (depending on the nature of hydrazine, hydrazine or chloromethylDHPMs 1a–d). Final products 7a–h easily dissolve in methanol while compounds 3b–s dissolve in the mixture 2-PrOH : DMF 1:1. Thus the reaction mixtures, containing high *ratio* of both products were washed with warm MeOH separating products of 7 type leaving products of 3 type for further crystallization. Depending on the physical characteristics, compounds 3b–s were purified with recrystallization either from 2-PrOH : DMF (4:1) or MeOH. It is worth mentioning that the crystallisation of the reaction mixture led to obtaining the product that forms the major amount of the reaction mixture.

Full physical-chemical data on the compounds 3b–s and 7a–h are given in the tabl. 2 and 3 correspondingly.

Synthesis of *4-(3-nitrophenyl)-4,6-dihydropyrimido[4,5-d]pyridazine-2,5(1H,3H)-dione (5)*. 0.05 mole of compound 3a was heated under reflux in 5 mL AcOH for 6 h and then allowed to stand at ambient temperature for 48 h. Yellow crystalline precipitate formed was filtered off, washed with 10 mL of EtOH to give pure compound 5.

Crystal data: $C_{13}H_{11}N_5O_4$, M 301.27, triclinic, space group P-1, a = 7.9891(9), b = 8.2345(9), c = 10.5430(12) Å, α = 102.894(5)°, β = 109.131(5)°, γ = 91.500(4)°, V = 635.03(12) Å^3, Z = 2, d_c = 1.576 g·cm^{-3}, μ = 0.121 mm^{-1}, $F(000)$ = 312, crystal size ca. 0.22×0.30×0.46 mm. The intensities of 6193 reflections were collected (2243 unique reflections, R_{merg} = 0.0296) within the range of $2.11 \le \theta \le 26.42°$ using MoK_α-radiation (λ = 0.71078 Å). The multiscan absorption correction (the ratio of minimum to maximum apparent transmission is 0.799250) was applied. The structure was solved by direct methods and refined by the full-matrix least-squares technique in the anisotropic approximation for non hydrogen atoms using the SHELXS97 and SHELXL97 programs [4, 5]. All hydrogene atoms were located from difference Fourier sinthesys and refined isotropically. In the refinement 2243 reflections (1637 reflections with $I \le 2\sigma(I)$) were used. Convergence was obtained at R1 = 0.0677 and wR2 = 0.1096, for all reflection and R1 = 0.0436 and wR2 = 0.0974, GOF = 1.019 for observed (243 parameters; observed/variable ratio 6.74; the largest and minimal peaks in the final difference map 0.19 and –0.27 e/Å^3, weighting scheme is as follows: $\omega = 1/[\sigma^2(Fo^2) + (0.0475P)^2 + 0.2689P]$, where $P = (Fo^2 + 2Fc^2)/3)$.

Yield 83 %, mp 253 °C. IR (KBr): 1330, 1530 (NO_2); 1620 (C=C); 1670 (C=O); 2300–3280 (NH). ^{1}H NMR (400 MHz, DMSO-d_6): 13.02 [*s*, 1 H, CO-NH], 8.18 [*m*, 3 H, Ar], 8.05 [*s*, 1 H, CH=N], 7.79 [*d*, ^3J(H,H) = 8.0 Hz, 1 H, Ar], 7.66 [*m*, 1 H, Ar], 5.56 [*d*, ^3J(H,H) = 2.6 Hz, 1 H, CHNH], 3.27 [*s*, 3 H, NCH_3].

Anal. Calcd. For $C_{13}H_{11}N_5O_4$: C 51.83; N 23.25. Found: C 51.82; N 23.24.

РЕЗЮМЕ. Исследована реакция взаимодействия 5-карбэтокси-6-хлорметил-3,4-дигидропиримидин-2-(1*H*)-онов с N,N'-динуклеофилами на примерах гидразингидрата, монозамещенных гидразинов и гидразидов карбоновых кислот. Установлено, что реакция протекает как нуклеофильное замещение галогена N,N'-динуклеофилом с последующей гетероциклизацией исходного пиримидина в производные пирроло[4,3-*d*]пиримидина и пиридазино[4,5-*d*]пиримидина.

РЕЗЮМЕ. Досліджено реакцію взаємодії 5-карбетокси-6-хлорометил-3,4-дигідропіримідин-2(1*H*)-онів з N, N'-динуклеофілами на прикладах гідразингідрату, моно-

заміщених гідразину і гідразидів карбонових кислот. Встановлено, що реакція проходить як нуклеофільне заміщення галогену N,N'-динуклеофілом з наступною гетероциклізацією вихідного піримідину в похідні піроло[4,3-*d*]піримідину та піридазино[4,5-*d*]піримідину.

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Received 23.11.2009

УДК 547.722:541.127

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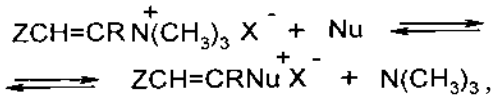
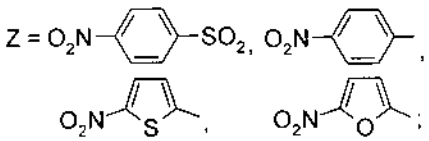
ВЛИЯНИЕ СТРУКТУРЫ ЧЕТВЕРТИЧНЫХ ТРИАЛКИЛВИНИЛАММОНИЕВЫХ СОЛЕЙ НА СКОРОСТЬ ИХ РЕАКЦИЙ С ТРИЭТИЛАМИН-N-ОКСИДОМ В АЦЕТОНИТРИЛЕ

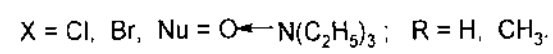
Изучена кинетика реакций триэтиламин-N-оксида с рядом виниламмониевых солей $Z–CH=CRN^+(CH_3)_3 \cdot Hal^-$ в ацетонитриле при 25—55 °С. Проведена количественная оценка влияния структуры активирующей группы Z и метильного заместителя R в α-положении к уходящей группе на скорость протекания исследуемых процессов. На основании полученных данных сделан вывод о реализации механизма присоединения-элиминирования в обменных процессах с участием триалкилвиниламмониевых солей.

Исследование кинетики и механизма реакций несимметричного фрагментарного обмена в винилониевых солях представляет значительный интерес, поскольку на их основе могут быть реализованы эффективные каталитические системы для процессов S_NVin-замещения [1].

В настоящей работе была поставлена задача количественно оценить влияние структуры активирующей группы и метильной группы в α-положении к уходящей группе в субстрате на скорость реакции фрагментарного обмена в винилониевых солях. С этой целью в данной работе была изучена кинетика реакций ряда виниламмониевых солей $ZCH=CRN^+(CH_3)_3 \cdot X^-$ с триэтиламин-N-оксидом в ацетонитриле при 25—55 °С:



где 



Полученные константы скорости второго порядка (первого по каждому из реагентов) приведены в таблице. На основании этих данных различные активирующие группировки Z по интенсивности их воздействия на подвижность уходящей триметиламмониевой группы можно расположить в следующий ряд: